REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS AND AMENDMENTS

Claims 3-7 were pending in this application when last examined.

Claims 3-7 were examined on the merits and stand rejected.

Claim 3 is amended to incorporate the limitations of claims 5 and 7. Support for these amendments can be found in claims 2 and 5 as filed. Claim 3 is further amended to recite that ingestion of a meal does not significantly alter the bioavailability or maximum plasma concentration of the active principle. Support for this amendment can be found on page 4, line 29 to page 5, line 5 and on page 22, lines 1-11, of the specification as filed.

Claims 5 and 7 are cancelled without prejudice or disclaimer thereto.

Claim 8 is added. Support for this claim can be found on pages 20-22 of the specification as filed.

Claims 3-4, 6 and 8 are pending upon entry of this amendment.

No new matter has been added.

II. PRIOR ART

Applicants respectfully note that Fanara et al. (US Patent Application No. 2002/0110596 A1, Document AB in the November 30, 2005 IDS) recites pharmaceutical compositions composed of an immediate release and a delayed release portion. Fanara et al. further discloses efletirizine. Applicants thus respectfully submit that Fanara et al. is the closest art of record.

II. OBVIOUSNESS REJECTIONS

A. Rejection of claims 3-5 and 7

Claims 3-5 and 7 were rejected under 35 U.S.C. § 103(a) as being obvious over Sunshine et al. (US 4,464,376) in combination with Kreutner et al. (US 5,869,479). Please see page 2 of the Office Action. Please also note that page 2 of the Office Action

contains a typographical error and should read claims 3-5 (instead of claims 1-5) remain rejected.

This rejection is respectfully traversed as applied to the remaining amended claims for the reasons noted in the previous response and for the following reasons.

Claim 3, the only remaining independent claim, is directed towards a pharmaceutical composition of efletirizine in the form of a two layer tablet with at least one fraction that allows immediate-release of efletirizine and at least one fraction that allows prolonged-release of efletirizine. Claim 3 is amended to limit the claimed pharmaceutical composition to ratios and ranges of the prolonged-release and immediate-release as indicated by the equations and ranges given. Finally, claim 3 is amended to recite "ingestion of the pharmaceutical composition before a meal or after a meal does not significantly alter either the bioavailability or maximum plasma concentration of the active principle."

The inventors have unexpectedly discovered that ingestion of the claimed pharmaceutical composition before a meal or after a meal does not significantly alter either the bioavailability or maximum plasma concentration of the active principle. This unexpected property is shown in Example 5 on page 22 of the specification. This property is not observed for immediate-release compositions as demonstrated in Example 4 on page 20 of the specification. Please see the attached 37 C.F.R. § 1.132 Declaration indicating this is an unexpected property of the pharmaceutical composition of the amended claims.

Furthermore, the claimed invention, as amended, relates to a modified-release pharmaceutical composition for administering an effective amount of efletirizine in order to rapidly obtain both an effective plasma concentration and maintenance of a minimum effective concentration over a prolonged period. In order to obtain such a pharmacokinetic profile, the claimed composition comprises at least two fractions containing the active principle. The first fraction allows immediate-release of the active principle and the second allows prolonged-release of the active principal.

A skilled artisan could not look to the literature and effectively compare efletirizine with other antihistamines such as loratadine and cetirizine, due to efletirizine's very specific pharmacokinetic characteristics (including half-life, plasmatic

elimination, oral clearance, etc.) For example, loratadine is a long acting drug exhibiting a dose-related rapid onset inhibition of the histamine-induced skin wheal and flare response in humans. Loratadine is apparent in the plasma 2 hours after ingestion and persists throughout the 24 hour observation period. The loratadine elimination half-life (t 1/2b) ranges from 7.8 to 11 hours; the descarboethoxyloratadine half-life ranges from 17 to 24 hours; and the cetirizine half-life ranges from 6.5 to 10 hours. Thus, these antihistamines already possess pharmacokinetic characteristics suitable for single daily doses and a skilled artisan would not examine such literature for obtaining daily dose pharmaceuticals containing principals with significantly shorter half-lives such as efletirizine, which has a half-life of 2.5 to 3.5 hours.

Efletirizine, unlike loratadine, does not persist throughout the 24-hour observation period. Consequently, a very specific galenic composition is required to obtain a daily dose tablet. Moreover, due to the pharmacokinetic characteristics of loratadine, a skilled artisan cannot merely replace loratidine with efletirizine in a galenic composition containing loratadine as an active ingredient and obtain a similar pharmacokinetic profile.

It has been established that prolonged-release pharmaceutical formulations commonly used by those skilled in the art and applied to efletirizine have the disadvantage of only slowly reaching an effective plasma concentration and, therefore, of delaying the therapeutic action of the active principle. In addition, it has been noted that such prolonged-release formulations, compared to the administration of two immediate-release doses of efletirizine 12 hours apart, induce a decrease in the maximum plasma concentration of efletirizine and also a decrease in its bioavailability. In fact, the various studies carried out have also revealed that efletirizine exhibits better absorption in the upper portions of the gastrointestinal tract.

With the composition of the claimed invention, it is possible, in order to relieve the patient as quickly as possible, to rapidly provide him or her with a therapeutically effective dose of efletirizine while simultaneously maintaining an effective minimum concentration for an extended period, preferably around 24 hours. In addition, all these conditions are met while maintaining bioequivalence with two administrations of 5 to 25 mg of efletirizine in an immediate-release form, given 12 hours apart. As shown in the table in Attachment B with the Declaration, there is only a small zone of acceptable

combinations of immediate-release/prolonged-release efletirizine that will exhibit the required AUC and C_{max} levels. Pages 14-20 of the specification demonstrate extensive experimentation was required to determine the necessary amounts of immediate-release/prolonged-release efletirizine to obtain these pharmacokinetic properties.

Thus, Sunshine et al. in view of Kreutner et al. do not disclose or suggest the claimed composition is unexpectedly resistant to alterations in C_{max} and AUC of the principle caused by patients eating food prior to ingestion of the pharmaceutical. Further, Kreutner et al. would not be used by a skilled artisan to develop the claimed invention because Kreutner et al. only gives working examples of antihistamines with long half-lives in long acting pharmaceutical preparations, which do not teach a skilled artisan how to use short half-life principals, such as efletirizine, in long acting pharmaceuticals as claimed in amended claims 3-4. Finally, the cited art does not teach or suggest how to make a combination prolonged-release/immediate-release efletirizine composition bioequivalent to two 12 hour doses of immediate-release efletirizine that quickly reaches an effective amount in the serum and maintains an effective amount in the serum for extended periods.

Thus, for the reasons given above as well as in the attached 132 Declaration, Applicants respectfully submit the above-noted references do not render amended claims 3-4 obvious and therefore this rejection should be withdrawn as applied to the amended claims. Applicants also respectfully note this rejection should not be applied to new claim 8 for the reasons given above.

Applicants further note that Fanara et al. does not render the amended claims or new claim 8 obvious or anticipated for reasons given above. In particular, in light of Fanara et al. it is still surprising and unexpected that ingestion of the claimed pharmaceutical formulation before a meal or after a meal does not significantly change either the bioavailability or maximum plasma concentration of the active principle.

B. Rejection of claim 6

Claim 6 was rejected under 35 USC § 103(a) over Sunshine et al. in view of Kreutner et al. and in further view of Guy et al (US 3,906,086). See page 2 of the Office Action.

This rejection is respectfully traversed as applied to the amended claims.

Claim 6 is directed towards the pharmaceutical composition of claim 3 wherein the prolonged-release fraction contains less than 5% by weight of basifying agent.

For the reasons given above, Sunshine et al. in combination with Kreutner et al. does not render amended claim 3 obvious. Thus, Sunshine et al. in view of Kreutner et al. and in further view of Guy et al does not render claim 6, which is dependent on claim 3, obvious.

Furthermore, the inventors have surprisingly found that despite the low level of basifying agent in the pharmaceutical composition of claim 6, *in vivo* absorption is constant regardless of pH. Thus, as demonstrated on page 22 of the specification, the coefficient of variation of the AUC (bioavailability) after administration of the claimed composition is 23% and 17% while fasting and after a meal, respectively. This is contrary to what had been observed *in vitro* in the dissolution test described in PCT/BE98/00033 as well as the AUC (bioavailability) data for immediate-release efletirizine while fasting and after a meal shown in Table 11 on page 20 of the specification.

Thus, Sunshine et al. in view of Kreutner et al. and in further view of Guy et al. do not disclose or suggest the invention of claim 6 is unexpectedly resistant to variations in bioavailability caused by changes in pH.

Thus, for the reasons given above, the above-noted references do not render claim 6 obvious and Applicants respectfully submit this rejection should be withdrawn as applied.

C. Conclusion

In view of the above, the rejection of claims 3 and 4 as amended under 35 U.S.C. §103(a) as obvious over Sunshine et al. in light of Kreutner et al., and the rejection of claim 6 under 35 U.S.C. §103(a) as obvious over Sunshine et al. in view of Kreutner et al. and in further view of Guy et al. are untenable and should be withdrawn.

CONCLUSION

In view of the forgoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

Monique BERWAER et al.

By: _____
Warren M. Cheek, Jr.
Registration No. 33,367
Attorney for Applicants

WMC/WRS/mjw
Washington, D.C. 20006-1021
Telephone (202) 721-8200
Facsimile (202) 721-8250
February 23, 2007

ATTACHMENTS

1. Rule 132 Declaration (executed)
2. Copy of pages 20-22 of the specification
3. Attachment B